

Treatment of fungal *Candida* infections with natural origin medicines

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ABSTRACT:

Natural medicines and in specially herbs spices and extracts for treatment of various diseases were the first medicines used from immemorial times. In treatment of fungal infection the traditional medicine provide a lot of possible extracts from plants with proved effects to cure superficial infections. This work reviews shortly the main remedies from alternative medicine used in different traditional and modern medicine from all over the world and new researches on the efficiency of the old methods of treatment against *Candida* infections. One of the targets of this paper is to describe the most interesting and active plant extracts in order to be use as alternatives to chemical antifungal products, in treatments against *Candida* species infections.

Key words: *Candida* infections, medicinal plant extracts, natural medicines, alternative medicine

INTRODUCTION

The natural plant extracts are mentioned in very old medicine treatise from Chinese and Indian, Roman Empire and Greek antiquity, Mediaeval Europe and Arabic world medicines. *Candida* infection is ones of the most disturbing infections and is practically spread in communities and hospitals as nosocomial infection, producing from superficial infections to disseminated severe infections and candidemia. Many plants with medicinal applications from different countries are still used as day to day medicine including antifungal [1]. Their MIC (minimum inhibitory concentration) and their antifungal activities can be characterized after CLSI and AFTS EUCAST standards the most used standards in the world. Even WHO consider traditional medicine like an alternative source of pharmaceuticals for modern medical cure. Some countries in development rely on them because of the low income of their citizens and lack of synthetic pharmacy products. The modern scientific methods of extraction and purification of the extracts, the use of the spectroscopic and photometric methods to identify extracts content and the quantity in which they are presents in the extract. A problem is to choose between some extracts containing same substances but in different amounts. Another problem is to consider the extracts containing no or less possible frequent allergens.

PLANT EXTRACTS

This is an extended examples section discussing the main results and updates regarding the effects obtained with different plant extracts in the treatment of human fungal infections. Generally speaking most of the extracts are mixtures of different compounds, some having together synergic effects.

There are in principle, aqueous extracts, ethanolic and methanolic extracts or others. Due to the nature of the solvents, the extracts content can suffer important variations. We present here some families of compounds used in anti-infectious therapies.

The triterpenoids saponins from the family of gymnemic acids are obtained from the leaves of *Gymnema sylvestre* R. Br. demonstrated to be an inhibitor of the transition phase from yeast to hyphal form. The transition from yeast to hyphal form depends on temperature pH, presence of serum, concentration of CO₂ and amino- acids [2] and the effect was dose-dependent. Alicine (2-propene-1-sulfinothioic acid, S2-propenyl ester C₆H₁₀O₂) is a compound found in garlic and have demonstrated antimicrobial properties (Gram negative bacteria), antifungal against *C. albicans*, anti-parasitic, and even antiviral activity due to the reaction with the thiol groups of the enzymes like alcohol dehydrogenase, RNA polymerase and thio-redoxin reductase [3].

Flavone and flavonoids.

The extract obtained from *Syngonanthus nitens* (Bong.) Ruhl. The compound was tested against *C. albicans* isolated from patients with vulvo-vaginal candidiasis in vitro and in vivo. The extracts contains flavonoids and flavone derivatives that inhibits the transition phase from yeast to hyphal form lacking cyto toxic and hemolytic activity [4]. The authors consider that the ointment with extract in concentration of 0, 5, and 2 % tested on rats are efficient in such infections. The aqueous and chloroformic extracts of *Tulbaghia alliacea* (L.f.) Thunb and *Tulbaghia violacea* Harv. from South Africa were used as antifungal against *Saccharomyces cerevisiae* L. the first having a half life killing effect in 2 hrs due to their content of marasmicin with a clear anti *Candida* effect in vitro

[5]. *Pogostemonis* Herba (*Pogostemon cablin* Blanco- Benth) extract was tested for its' anti *Candida* effect using as a control the voriconazole showing both similarly results -MIC 3.1µg/mL to 50µg/mL [6]. The topic administration of pogostone at 1-4 mg/kg was effective, superior to voriconazole at 4 mg/kg and it is easily absorbed by mucosa and its toxic dose is much greater than the therapeutic doses (355 mg/kg for mouse). The *Aloe vera* extract, included in Sabouraud agar culture medium in concentration of 10% (g/vol.) is able to inhibit the germinative tube formation (to *Candida albicans*), in proportion of 90-100% [7]. The extract of *Syngonanthus nitens* (Bong.) Ruhl. contain flavones derivatives [8] with inhibition effect of the transition from yeast to filamentous form on the strains isolated from patients with *Candida* vulvovaginitis. The treatment trial with a cream with doses of 0, 5, 1 and 2% extract was tested on female rats for the beginning.

Terpenes and terpenoids

The betulin-lup-20 (29)-ene 3-beta-28-diol) is a natural triterpene extractible from *Betula* bark and can be produce about 65 semi-synthetic compounds [9]. Derivative compounds (SC 047) were identified as efficient at concentrations of 6,25µM (Minimum Inhibitory Concentration), against one of many bacterial strains of *E. faecalis* and *S. aureus* and some compounds with activity against *C. albicans*. Some tests on hepatocyte cultures showed some derivatives have cytotoxic effects in different concentrations.

Phenols and derivatives

The polyphenols from *Pistachia vera* L. demonstrated to have antimicrobial properties on Gram negative strains (*E. coli*, *Pseudomonas aeruginosa*, *P. mirabilis* Hauser), Gram positives as *Listeria monocytogenes* (Murray et al) Pirie, *Enterococcus faecium* (Orla-Jensen) Schleifer et Klipper – Bälz), *Bacillus subtilis* (Ehrenberg) Cohn, *Staphylococcus epidermidis* (Winslow and Winslow) Evans, *S. aureus*) and antifungal properties against yeasts strains *Candida albicans*, *C. parapsilopsis* and fungi like *Aspergillus niger* van Thieg. [10].

Methanolic extracts of *Inula* species (*Inula helenium* L. ss.p *turcoracemosa* Grierson, *I. montbretiana* D.C. and *I. viscose* (L.) Aiton) was tested for its antioxidant, antifungal and antimicrobial activity [11] against *S. aureus* Rosenbach, *E. faecalis*, *E. coli* (Escherich, Migula) Castellani et Chalmers), *Pseudomonas aeruginosa* (Schröter) and against the yeasts *Candida albicans* and *Candida tropicalis* Berkhout 1923. These extracts have an effect against Gram positive bacteria and against yeasts due to their phenolic compounds – caffeic acid,

rutin, quercetin, lutelin and kaempferol. The polyphenols are complex phenolic compounds and they are effective against biofilm formation and proteasome. *Candida* inactivation by the polyphenols obtained from *Tea sinensis* L. [12] was demonstrated.

Saponins

The saponins are compounds having antifungal activity too. The steroidal saponins and steroidal sapogenins were isolated from some monocotyledonates plants and were tested on *C. albicans*, *C. glabrata*, *C. krusei*, *Cryptococcus neoformans*, *Aspergillus fumigatus* (Yang et al. 2006). The extract from *Solanum chrysotrichum* Schltd. [13] is used in Mexico for the treatment of fungal infection of epithelium and mucosa under the form of metabolic extract containing saponins (SC2-SC6). Extracts with spooning SC2 (conc.1,89 mg/l), was tested against vaginal infections with *C. albicans* (CP. Robin) Berkhout (1923), using as control ketoconazole 400 mg/l. on 100 persons having symptoms of fungal vaginitis (a patients treated with natural medicine and a control treated with classical medicines). The two groups of patient's treatment showed efficacy of 57, 14% to 72, 5% of total cases, and the second with efficacy of 62, 8% and 97%, and 5% respectively. The triterpenoid saponins from family of gymnemic acids are obtained from the leaves of *Gymnema sylvestre* R. Br. demonstrated to be an inhibitor of the transition phase from yeast to hyphal form.

The steroidal saponins activity due to the aglicon part of their molecules and of their monosaccharide structures in the polysaccharide chains. The authors identified ten saponins with antifungal effect. Some authors [14] isolated eight saponins from *Tribulus terrestris* testing them on effect against 6 fluconazole resistant strains of *Candida albicans*, *C. glabrata*, *C. parapsilopsis*, *C. krusei*, *C. tropicalis* Berkhout TTS 12 and TTS15 were demonstrated to be the most efficient against *C. albicans* in vitro with a MIC of 4.4.-9 µg/ml, and in vivo against vaginal *Candida* infection. TTS 12 acts for cell membrane destruction and inhibition of hyphae formation. SC2 saponins obtained from *Solanum chrysotrichum* a Mexican plant were tested on vulvovaginal candidiasis.

Other compounds and extracts.

Here we exemplify some other compounds and different extracts effects. Generally speaking the general plants extracts contains one principal product with curative effects or a complex of substances with curative effects acting together. Some of them can be use to obtain further some important main components.

Miltephosines is a compound class with broad antifungal effect and can be used against fungal infections as genuine or modifying the structure of miltefosine chains [16]. The tested compounds were derivatives of it, the 3a (2-benzyl dimethylammonio)-ethyl-hexadecyl phosphate; 3d-2-dimethyl-(4-nitrobenzyl)-ammonium-ethyl-hexadecyl-phosphate and 3e-2 (diethyl-(4-methoxybenzyl)-ammonium)-ethyl-hexadecyl-phosphate were the best against pathogenic fungi *C. albicans*, *C. glabrata*, *C. krusei* (Castellani) Berkhout, *A. fumigatus* Fres., *Cryptococcus neoformans*, with a MIC of 2.5-5 µg/mL but the researches require some toxicological tests too.

A good treatment strategy is the inhibition of biofilm formation on mucosal surface with 4 type of polyketide-glycosides obtained from the fungus *Bionectria ochroleuca* (Schwein.) Schroers et Samuels) co-cultivated together with a *Penicillium* species [17]. The extracts from African plants *Uvaria chamae* P. Beauv., *Spondias mombin* L. and *Combretum racemosum* P. Beauv. Contains many active substances –alkaloids saponins, oils, tannins, flavonoids, terpenoids and others. The aqueous and polar solvents (methanol, n hexane) extracts are active against *Candida* species and the results of MIC tests of *Uvaria* extracts are comparable with the ketoconazole values [18].

Azadirachta indica (also known as “Neem”) is a plant used in many domains like control of diseases and pests in agriculture and not only. *Azadirachta* extracts in hexane, chloroform, dichloromethane, methanol, acetone, ethanol and water were tested on *Candida* isolates from the immunocompromised patients [19]. The aqueous, chloroformic and methanolic extracts were not effective but the ethanolic and hexane extracts were positive results in all tests performed.

The traditional method in using old recipes with natural products were investigated in India like the old Siddha medicine formulations based on plants revealed that the affinity of plant extracts was even greater than modern classical antifungal like fluconazole and clotrimazole used in topic formulations [20].

The anticandidiasis activity of extracts obtained by steam distillation of *Origanum hypericifolium* O. Schwarz et PH. Davis and *Salvia potentillifolia* Boiss et Heldr., ex Bentham were tested on their activity against 93 *Candida* clinical isolates (*C. glabrata*, *C. kefyr*, *C. albicans*, *C. tropicalis*, *C. krusei*, *C. parapsilopsis*) and extracts of *S. potentillifolia* was efficient against two strains of *C. glabrata* [21] and

the extract from *O. hypericifolium* was effective against *C. albicans* and *C. tropicalis* strains. The 18-beta-glycyrrhetic acid, extract from *Glycyrrhiza* roots is able to induce the stimulation of Th1 cells activity and of the immune response of these cells [22].

The extract of peels of pomegranate was used as aerosols for disinfection of air and surfaces [23]. Methanolic extract from *Godmania aesculifolia* (Kunt) Standl. from roots contains antifungal compounds-carvacrol diglicoside 3, 4-dihydroxy 2-(3-methylbut-2-en-1-yl) 3,4-dihydronaphthalen-1(2H)-one, and lapachol isolated and characterized by mass spectroscopy the last with an evident antifungal effect against *Cryptococcus neoformans* (San Felice) Vuill. and moderate against *Candida* strains [24] (Tamayo-Castillo et al, 2013).

Many plants from Turkey were investigated for their antifungal effect of their methanol and chloroform extracts (*Gallium verum* L., *Mentha piperita* L., *M. longifolia* (L.) Huds., *Salvia limbata* C.A. Meyer, *Prangos ferulaceae* (L.) Lindl., *Artemisia austriaca* Jacq., *Plantago lanceolata* L. and *Urtica dioica* L. against over 90 strains of *C. albicans*, *C. tropicalis*, *C. glabrata* (H.W. Andersson) SA Mey et Yarrow from clinical samples and against standard strains from ACC collection by MIC method [25]. In Thailand studies of screening of local flora for their antifungal effect were performed. Methanolic extracts from fruits of *Hibiscus sabdariffa* L, roots of *Trigonostemon reidioides* (Kurz), *Usnea siamensis* Vain all plant, and rhizomes of *Boesenbergia rotunda* (L.) Masf., stems of *Albizia myriophylla* Benth with antifungal activity against *C. albicans*, *C. glabrata*, *C. guilliermondi*, *C. krusei*, *C. parapsilopsis* and *C. tropicalis*. The extracts of *A. myriophylla* has a MIC of 100-500 µg/ml and had a rapid action against all the strains and the reduction of CFU's obtained was 99% in 2 hours [26]. Solvent extracts of aerial part and flowers of *Tagetes patula* obtained by percolation method with solvents were tested on *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. albicans*, *C. parapsilopsis* in vitro, and the methanolic and ethanol extracts were active against the investigated strains-MIC 78.12 µg/mL (aerial parts methanolic extract); 51.08 µg/mL (methanolic flower extracts), - 39.06 µg/mL flower (ethanolic extract) 78.12 µg/mL (ethanolic aerial extract) being effective at concentrations of under 100 µg/mL. *Tagetes patula* contains secondary metabolites as thiophenes, benzofurans, carotenoids and flavonoids. The extract can be used for their synergic activities together with classical antifungal [27].

Some extracts can be used like disinfecting substances in stomatology and as antifungal [29]. The authors tested the extracts of *Punica granatum* L., *Acacia nilotica* A.F. Hill-ssp nilotica, *Cuminum cyminum* L. and *Foeniculum vulgare* Mill. In vitro, by disk diffusion method using about 30 µl of extract on each and deposited on culture media observing the inhibition area. Most effective was the *Punica granatum* extract with an inhibition area of 22 mm. One type of the virulence factors, are the enzymes secreted by fungi which can be inhibited by plant extract containing flavonoids compounds- apigenin, kaempferol; alkaloids –berberine, ibogaine in topical formulations [29]. The methanolic extracts of *Elaeis guineensis* Jacq. (*Arecaceae*) has effect against *C. albicans* by growth inhibition and modification of the structure and morphology observed in TEM [30].

The extract obtained with dichloromethane from the bark of *Swartzia simplex* (Sw.) Spreng. contains a compound with antifungal activity against *Candida albicans*. The active substance was isolated and identified by HPLC micro-fractionation method in micro plaques with 96 wells and by autoradiography for their identification HPLC PAD method. Finally about ten compounds were obtained [31].

The root extract of *Morella serrata* (Lam) Killick-Myricaceae) was tested in 96 wells micro plates [32] for its antimicrobial and antifungal activity containing flavonoids tannins, saponins, terpenoids and steroids the extract inhibited bacteria and suppressed the growth of *Candida* species and *Trichophyton* at about 0,13 and 3,13 mg/mL MIC [32].

Interesting fact is that the cabbage fermented by the *Pectobacterium atrosepticum* (van Hall) Gardan et al. strain is effective against *Candida* demonstrated by disk susceptibility test (500µg) production of inhibition area of 10-13mm, at a concentration of 2000µg/ml and have therapeutic effect [33]. The same bacteria has an effect of producing fermented products from tomato plants having a minimum inhibitory concentration of 250ug/mL, against *Candida glabrata* strains. Amento-flavones isolated extracted by ethyl-acetate, from *Selaginella tamariscina* (P. Beauv.) Spring have antifungal effect inducing cell apoptosis events –fragmentation of DNA, ROS accumulation in the cell, release of phosphatidylserine and stimulation of mitochondria dysfunction by radical hydroxyl formation [34].

Plant defensins like NaD1 are compounds playing the role of plant defense against pathogenic fungi

[35]. In the peculiar case of defensins obtained from *Nicotiana glauca* flowers (producing membrane and cell wall structure destruction of the yeasts) producing permeability of membrane and by their penetration in cytoplasm, they stimulate the production of reactive oxygen species which will destruct the cells.

The *Andropogon paniculatus* (Lam.) Wall ex Nees extracts are active against fungal infections of the skin facts demonstrated by in vitro tests [36] – dichloromethane and methanolic extracts, the first with a MIC 100 µg/mL against *Candida albicans* and *C. tropicalis* and against *Microsporum canis* E. Bodin, and the methanol extract MIC 150 µg/mL against *C. tropicalis*/ MFC of the dichloromethane extract against *M. canis*, *C. albicans*, *C. tropicalis* and *A. niger*, (250 µl/mL) and the methanolic extracts have a MFC 250 µl/ml against fungi *Trichophyton* sp., *M. canis*, *C. albicans*, *C. tropicalis* and *A. niger*. The extract contains substances responsible for antifungal activity – 3-O-beta-D-glycosyl-14-deoxy-andro-graphiside, 14--deoxy-andro-grapholide, and 14-deoxy-11, 12-di-dehydro-andrographolide.

Other group of products obtained from plants are the proto-antho-cyanidins extracted from cranberries (species of *Vaccinium* like *V. erythrocarpum* Michx. *V. macrocarpum* Ait., and *V. oxycoccum* L.) acting like inhibitors in biofilm formation in urinary tract infections [37], at about 16 mg/mL are able to reduce the biofilms formation. In table 1 some other extracts with anti *Candida* activity can be seen.

MECHANISM OF ACTION OF NATURAL PRODUCTS

Practically the natural products (extracts from plants from different parts-roots bark, rhizome, flowers, herb, leaves, fruits or seeds, performed with alcoholic solvents methanol, ethanol, other polar organic solvents-dichloromethane, benzene, toluene) aqueous extracts obtaining products (tincture, extracts, decocts). The extracts contain a lot of active substances including some with antifungal effects. Extracts of *Brucea javanica* L. (Merr) and *Piper betle* L. [38] demonstrated an anti-adhesion activity on *Candida* species (*C. albicans*, *C. parapsilopsis* Ash. and *C. tropicalis* Berkhout). The properties of adherence were tested as hexadecane adsorption and the reduction of adherence was about 80% by use of *P. betle* extract [39].

Anyway part of the healing action can be due to the synergic effects of some active compounds. Compounds like terpenoids (linalool, eugenol, citral, linalyl-acetate, benzyl-benzoate and citronellal) were tested online against *Candida* and

practically showed activity against this fungus by inhibition of their general activity and metabolism and transition from one form –yeast to another-filament form [42].

CLASSICAL AND ALTERNATIVE MEDICINES USES AND LIMITATIONS

Plant extracts and alternative remedies are used from immemorial times against infections and to other types of diseases, have an extraordinary revival in modern times (see table 1). The business with alternative medicine in USA for example will be in 2015 more than 13 billion dollars other sources statement showed about more than 34 billion dollars [43] in 2013 following an USA today report. The new tendency was enhanced by the bio trend all over the world and of course all kinds of alternative medicine gurus in works mixing lack of professionalism and popular enthusiasm publish advices in brochures, Sunday and women magazines attracting clients for naturist shops. In the same time, the lack of real standards for natural medicines from alternative market is still a problem for the official agencies of drug control and accreditation and the lack of a real constant content of the natural extract (they can contain many hundreds compounds), and the lack of reproducible results make the skepticism of real professionals in medicine and pharmaceutical industry. Other source of issues problems is the enthusiasm of some researchers which try hard to demonstrate the efficiency of natural extract and practically highlight only the good results. The organization-NGO in generally supporting the natural food and medicines lack practically the professionalism and use a kind of semiprofessional slang to support their purposes. Plant extracts are a play ground for professionals and in the same time of some enthusiastic non-professionals interested in the promotion of so called Green Products in all the area of nutrition, pharmaceuticals and cosmetics.

There are a lot of projects regarding the natural plant extracts for research in Europe and other part of the world. The developing countries with a reduce possibility to use expensive pharmaceutical products are interested to develop the alternative products. We can note the Chinese and Indian experiences, which extended the use and the modern researches upon natural extracts. The criteria for selecting a certain plant for use as therapeutic alternative or complementary medicine is to have enough content of the antifungal active substances, to be easy to separate and to be found in nature or cultivation in quantities to justify the set up of an industrial process and to have a decent and accessible price.

Even with the admitted limits, the applications of natural products and plant extracts are an alternative or better complementary medication to the industrial chemical or organic synthesis, or semi-synthesis medicines from the pharmaceuticals industry. The clinical physicians but in special the general practitioners family must be instructed in both allopathic and alternative medicine in order to select for one or others in function of practical aspect of every investigated case of infection. What characteristic should have a natural product to be considered for a real therapy.-the natural source must be well known, and to have a certain geographical extent we cannot rely only on local or endemic flora because we cannot have enough material for a real industrial production; to have a known content of bioactive compounds ;they must be in appropriate amount in the natural material; to be somehow constant as content between some limits in order to be efficient; this content must be easy to obtain by extraction; to have advantages comparing with synthetic medicines; to keep its therapeutic characteristics long time; to be easy to pack and to apply; to be free of allergens; to have no major counter indications in therapies; to be efficient for its task; to be recommended by professionals.; and of course to have validated studies regarding their efficiency versus modern therapies.

There are lots of requirement for such medicines but we must assure for patients high quality treatments. The importance of standardization of natural origin medicine is showed by medicament agencies and different organization in entire world and in special in Europe. WHO issued some guides and 4 volumes containing monographs of selected medicinal plants. The European Directorate for Quality of Medicine and Health Care issues different guides, indications for European Pharmacopoeia, and regulations and standards in the field of pharmaceuticals. A project of Association of African Medicinal Plants Standards (AAMPS) is the standardization of traditional natural origin medicines and issued an African Herbal Pharmacopoeia [44]. The European Directive on Traditional Herbal Medicinal Products (THMPD) the Directive 2004/24/EC are regulations of natural plants products for human use and show the regulatory approval for traditional medicines on the territory of EU.

CONCLUSIONS

Candida is still a problematic infectious agent with effect from thrush and superficial infections, to severe disseminated candidemia and *Candida* infections in immunocompromised patients. The natural plant extracts demonstrated a certain effect

against the fungi with limitations, which qualified the natural extract as complementary remedies against fungal superficial infections. What is very clear preventive measure and treatments with synthetic chemicals and classical medicine products will be never replaced by this kind of natural products, but the last ones can be of a real help as adjuvant therapies in special in not severe cases and some superficial skin and mucosal infections. The practitioners must be instructed in natural products uses too and to be more flexible to its use. Further biochemistry and microbiology studies, also clinical researches are necessary in order to identify the target of the main active components of the essential oils or other type of natural extracts and products. Another issue for the future is the improvement of experimental protocols using a better randomised control trial for better comparable results and the demonstration of the value of modern natural therapies.

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Table nr. 1. Various extract of medicinal plants with anti *Candida* effects

Nr	Plant	Extract type	Content	Effect	References
1	<i>Matricaria chamomilla</i>	Methanol extract	azulenes	Inhibitory effect against <i>Candida</i> species Antioxidant activities	[45]Abdoul Latif et al., 2011
2	<i>Thymus viciosoi</i>	Extract	carvacrol, thymol and p-cymene	produce inhibition of filamentation of <i>C. albicans</i>	[42] Vale-Silva et al 2011.
3	<i>Abutilon theophrasty</i>	Extract	Hibisculide C	Antifungal properties damage membranes	[35]Hwang et al. 2013
4	<i>Solanum chrysotrichium</i>	Methanolic extract	saponins (SC2-SC6).	treatment of fungal infection of epithelium and mucosae	[14]Herrera-Arellano et al. 2013
5	<i>Gymnema sylvestre</i>	Extract	triterpenoids saponins from family of gymnemic acids	an inhibitor of the transition phase from yeast to hyphal form	[2]Vedyyappan et al., 2013
6	<i>Allium sp</i>	Extract	Alicine	antibiotic and antifungic effect	[3]Ankri et Mirelman, 1999. [46]Parvu et Parvu 2011
7	<i>Inula species Inula helenium ssp turcoracemosa, I. montbretiana and I. viscosa</i>	Extracts	Phenolic compounds caffeic acid, rutin, quercetin lutelin and kaempferol.	Antibacterial activity Antifungal activity <i>Candida albicans</i> and <i>Candida tropicalis</i>	[11]Gökbulut et al, 2013
8	<i>Tea sinensis</i>	Extract	polyphenols	<i>Candida</i> infections inactivation Biofilm formation inhibition	[12]Aladag et al 2009 [47]Evensen NA., Braun CP, 2009
9	<i>Brucea javanica</i>	Water Extract	Quassinoids main compounds and other 152 compounds	anti-adhesion activity of <i>Candida species</i> . Change the expression of hyphal wall protein Antitumoral activity	[39]Nordin et al, 2013 [48] Harun et al, 2013 [49] Zhao et al, 2014
10	<i>Piper betle</i>	Water extract and chloroform extracts	hydroxichavicol	Inhibition <i>Candida</i> species reduced the biofilm formation	[39]Nordin et al, 2013 [50]Ali I, et al. 2010
11	<i>Godmania aesculifolia</i>	Methanolic extract	-carvicrol diglicoside 3,4-dihydroxy 2-(3-methylbut-2-en-1 yl) 3,4-dihydronaphtalen -1(2H)-one,	antifungal effect against <i>Cryptococcus neoformans</i> moderate against <i>Candida</i> strains	[24] Tamayo-Castillo et al, 2013
12	<i>Syngonanthus nitens</i> (Bong.) Ruhl. (Extract	contains flavonoids and flavone derivative	Inhibits transition phase from yeast to hyphal form	[4]de Freitas-Araujo, e al, 2013.
13	<i>Tulbagia alliacea</i> and <i>Tulbagia violacea</i> compound named and having	Water and chloroform extracts	marasmicin	antiinfective effect against <i>Candida</i> strains in vitro	[5]Thamburan et al 2006
14	<i>Pogostemon cablin</i> Blanco- Benth.	Extract	pogostone	antifungal effects against <i>Candida</i>	[6]Li et al., 2012.
15	<i>Aloe vera</i>	Glycolic extract	Aloine, (an anthraquinone), lupol, salicylic acid, cinnamonic acid, phenols	Inhibition of germinative tube formation at <i>Candida albicans</i>	[7]Bernades et al, 2012 [46]Parvu et al, 2011
16	<i>Uvaria chamae</i> , <i>Spondias mombin</i> and <i>Combretum racemosum</i>	The watery and polar solvents (methanol, n hexane	alkaloids saponins, oils, tanins, flavonoids, terpenoids and others	active against <i>Candida</i> species	[18]Okwuosa et al. 2012

17	<i>Tagetes patula</i>	Extract methanolic and ethanolic	thiophenes, benzofurans, carotenoids and flavonoids	The extract can be used for their synergic activities together with classical antifungals <i>C.glabrata</i> , <i>C.tropicalis</i> , <i>C. krusei</i> , <i>C. albicans</i> , <i>C. parapsilopsis</i> in vitro	[27]Politi et al, 2013
18	<i>Azadirachta indica</i>	Extracts in hexane, chlorophorm, dichloromethane, methanol, acetone, ethanol and water	Nimonol, polyphenolic flavonoids-quercetin, beta sitosterol, 6-deacetylnimbin, azadiradione, nimbin, salannin and epoxy-azadiradione	Used against <i>Candida</i> isolates from the immunocompromised patients	[19]Charmaine et al, 2005 [51]Mahmoud et al 2011
19	<i>Swartzia simplex</i>	Dichloromethanolic extract	diterpenes afrormosin, polyphenols, 11,12-dihydroxy-15,16-dihydroswartziarboreol C; 15,16-dihydroswartziarboreol C; swartziarboreol A; B; C and E	antifungal activity against <i>Candida albicans</i>	[31]Favre-Godal, et al., 2013.
20	<i>Pistachio vera</i>	Extract	polyphenols	Antimicrobial and antifungal activity	[10] Bisignano et al, 2013
21	<i>Morella serrata</i> (Lam) Killick-Myricaceae	Extract	flavonoids, tannins, saponins, terpenoids and steroids	Antifungal activity	[32]Ashafa,2013
22	<i>Tribulus terrestris</i>	Extract	steroidic saponins	Against species <i>Candida albicans</i> , <i>C. glabrata</i> , <i>C. parapsilopsis</i> , <i>C. krusei</i> , <i>C. tropicalis</i>	[15]Zhang and coworkers 2005
23	<i>Solanum chrysotrichum</i>	Methanolic extract	SC2 saponins	Fungicide and Fungistatic activity against <i>Candia</i> species from vulvovaginal candidiasis patients	[14]Herrera-Arellano et al. 2013
24	<i>Nicotiana glauca</i>	Flower extracts	Plant defensins	cell wall structure destruction of the yeasts	[35]Hayes et al, 2013
25	<i>Andrographis paniculata</i> /	Dichloromethan and methanol extract	responsible for antifungal activity -3-O-beta-d-glycosyl-14-deoxy-andro-graphiside, 14--deoxyandrographolide, and 14-deoxy-11, 12-didehydro-andrographolide.	<i>Candida albicans</i> and <i>C. tropicalis</i> , <i>Microsporus canis</i> , -methanolic extract MIC150µg/ml against <i>C. tropicalis</i>	[36]Sule et al 2012
26	<i>Terminalia mollis</i>	Extract	-Friedelin -gallic catechin with epigallocatechin -3-O-methyl gallic acid 4'-O- α -rhamnopyranoside - Arjunolic acid with 2 α , 3 β , 23-trihydroxy-urs-12-en-28-oic	Some extracts active against <i>Candida</i> species	[52]Liu et al 2009
27	<i>Vaccinium oxycoccus</i>	Extract	Derived proanthocyanidins (PACs)	anti-adherence properties, treatment in UTI for prevention and/or treatment of <i>Candida</i>	[37]Rane et al 2013